Adrenal cortex hormones in male epileptic patients before and during a 2-year phenytoin treatment

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SUMMARY Serum levels of progesterone, cortisol and phenytoin as well as the excretion of 17-OHCS were determined in 45 male epileptics before and during 24 months of the therapy. A significant decrease of the hormones was found in untreated patients. Phenytoin administration caused further decrease of cortisol and its metabolite 17-OHCS levels and a compensation of progesterone serum concentration.

Investigations of the activity of hypothalamic-pituitary-adrenal cortex axis have been mainly concerned in aspects to the influence of anticonvulsants on adrenal cortex function. After long-term treatment patients have shown a decrease of serum and urinary levels of glicocorticosteroid hormones as well as a diminished adrenal cortex response to metapirone and dexamethasone.

The aim of this study was to determine whether the disease itself may have an influence on adrenal cortex function apart from the effect of therapy, with one frequently used antiepileptic drug, phenytoin. Adrenocortical hormones were determined before and during a 2 year period of anticonvulsant therapy.

Material and method

Forty five male patients, aged 20-49 years (mean age 32.4 ± 8.6) admitted for the first time to the Centre for Epilepsy at Zabrze and never before treated for epilepsy, were studied. Mean age of onset was 27.4 ± 11.3 years. In 26 patients the period between the first and the next seizure, after which the anticonvulsant therapy was introduced ranged from a few months to 1 year. In 14 other males the period was longer (about 2-4 years), and five cases had initial seizures in childhood with long-term remission without treatment.

In 60 patients the illness could be classified as primary generalised epilepsy. In the remaining 21 cases with known aetiological factors, partial or secondary generalised seizures and focal EEG changes, epilepsy was classified as secondary.

Most patients had tonic-clonic seizures; in nine cases temporal lobe seizures were observed, and in two of them together with tonic-clonic fits. During 2 years of observation 19 patients had rare seizures, about one per year (mild epilepsy), and in the remaining 24 patients the incidence of tonic-clonic seizures as well as temporal lobe seizures ranged from one to several in a month (severe epilepsy). In all the patients phenytoin was given in daily doses of 200-300 mg (mean 273.3 ± 128.0 mg) per day.

Hormone determinations were performed before treatment and then every third month during 2 years of phenytoin therapy (nine inter-ictal determinations in each patient). The control group consisted of 45 healthy male volunteers aged 20-49 years (mean age 39.1 ± 9.1). Blood samples were collected during 3 successive days and the mean of the results from these days were used. Serum progesterone and cortisol concentrations were measured by radioimmunoassay of samples taken between 8-9 am. Serum phenytoin levels were determined in the same blood samples. Twenty-four hour urinary excretion of 17-OHCS was estimated by spectrophotometry. The data were analysed statistically using Student's t test (p < 0.05).

Results

The individual results of hormonal determinations in untreated epileptic patients and in the control group are shown in fig 1. Mean serum hormone levels before and during phenytoin therapy in comparison with control values are given in table 1, and presented graphically in fig 2.

Progesterone serum concentration

Before treatment there were already more patients...
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Fig 1 Individual results of serum progesterone and cortisol levels, and 17-OHCS urinary excretion in untreated epileptic patients (P) in comparison with control group (C). ——— mean values.

Table 1 Mean progesterone and cortisol levels in serum and 17-OHCS in urine in 45 male epileptics and in control group. Serum phenytoin levels in patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>Progesterone nmol/l</th>
<th>Cortisol nmol/l</th>
<th>17-OHCS μmol/24 h</th>
<th>Phenytoin μmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration in</td>
<td>3</td>
<td>4.38 ± 1.95 [45]</td>
<td>395.58 ± 200.09 [34]</td>
<td>7.15 ± 3.95 [33]</td>
</tr>
<tr>
<td>Controls</td>
<td>4.36 ± 1.82 [45]</td>
<td>542.70 ± 220.07 [36]</td>
<td>10.40 ± 4.76 [38]</td>
<td>—</td>
</tr>
</tbody>
</table>

*p < 0.05, +p < 0.01, †p < 0.001.

Number of patients in brackets.

with lower progesterone serum concentration than in the control group (fig 1). Mean serum levels were significantly decreased before phenytoin therapy as compared with controls (p < 0.01), table 1. During drug administration the level of progesterone approached the normal value (table 1, fig 2). The proportion of patients with abnormal results, given in fig 3, was 33% of untreated patients, and after 24 months of phenytoin treatment decreased to 7%.

Cortisol serum concentration

Before therapy more patients with decreased serum cortisol level were found as compared with the control group (fig 1). Mean serum concentration of this hormone was evidently lower before treatment (p < 0.05) in relation to control values (table 1, fig 2). After 24 months 3 and 6 of phenytoin therapy cortisol serum levels further decreased (p < 0.01). Therapy continuation caused a certain increase in hormone levels.
and the results were closer to those found before treatment \((p > 0.05)\). The abnormal results were found in 46% of patients before treatment and in 19% during the first 12 months of therapy without further changes until the end of the observation (fig 3).

17-OHCS urinary excretion

The results showing lower urinary excretion of cortisol metabolite were found more frequently in untreated patients in control males (fig 1). Mean urinary excretion of 17-OHCS, significantly lower before therapy \((p < 0.01)\) further decreased during drug administration \((p < 0.01)\) in relation to control values (table 1, fig 2). In 33% of untreated patients abnormal results were found, and during therapy this percentage increased to 54% (fig 3).

Serum phenytoin levels

No correlation between the results of hormone determinations and serum phenytoin levels was seen (table 1). The lowest drug level found in the 3rd month of treatment could be associated with irregular drug usage by the patients.

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**Fig 2** Mean serum concentration of progesterone (P) - – – – cortisol (F) O – – – O and urinary excretion of 17-OHCS ▲ – – ▲ in comparison with control values, and serum phenytoin levels during the 24th month of therapy (in column).

**Fig 3** The percentage of epileptic patients with abnormal results of hormonal determinations (progesterone ■ cortisol □, and 17-OHCS ▼) during 2 years on phenytoin treatment. M, males; F, females.
Hormonal determinations and clinical features of epilepsy

Hormone levels before and during phenytoin therapy in relation to aetiology and the course of the disease are shown in table 2. Before treatment a slightly lower progesterone concentration could be noted in the group with known aetiology. Similarly, lower cortisol concentration and decreased 17-OHCS excretion were found in patients with known aetiological factors of epilepsy.

During therapy lower levels of progesterone were observed in patients with severe as compared with mild epilepsy. Cortisol concentration was slightly higher in patients with severe epilepsy after months 12 and 24 of phenytoin treatment, while urinary excretion of its metabolite (17-OHCS) decreased more in severe than mild course of epilepsy.

It may be noticed that in nine patients with temporal lobe seizures, the hormone levels were found to be more decreased as compared with those in patients with other types of fits, but the difference was not statistically significant.

Discussion

Alterations in hormonal concentrations found in our study before phenytoin treatment confirmed our hypothesis that the epileptogenic process itself may influence adrenal cortex function. This observation is in agreement with the suggestion of some investigators that endocrine dysfunction may be unrelated to anticonvulsant therapy. The reason for a significant decrease in all hormone determined before phenytoin administration is not clear. It may be explained by the influence of the aetiological factors which not only caused epilepsy but could also disturb the close functional and structural relationship between the central nerve system and the endocrine system, and in consequence diminished adrenocortical activity. This may be evidence by more frequent alterations in hormonal levels in patients with known aetiology of epilepsy; on the other hand, we have found greater hormone disturbances in patients with severe epilepsy connected with frequent tonic-clonic as well as temporal lobe seizures. Thus post-ictal focal changes should also be considered.

During phenytoin therapy further changes in cortisol and 17-OHCS levels were observed, which may indicate the effect of the drug on adrenal cortex function, stressed also by many other authors. After 3 months of phenytoin, decreased progesterone levels were observed, whilst after months 3 and 6 a further fall in the levels of cortisol and its metabolite was found. Continuation of phenytoin treatment caused some levelling of diminished cortisol serum concentration noted during the first 6 months, whilst the amounts of 17-OHCS still remained significantly low. Furthermore, the number of patients with abnormal cortisol levels decreased and the number of patients with lower 17-OHCS values increased during the 2 years of phenytoin therapy. This may be explained by the effect of the drug on extra-adrenocortical cortisol metabolism occurring in the liver, where phenytoin stimulates microsomal cortisol hydroxylation.

The results obtained after 2 years of anticonvulsant therapy are in agreement with the findings of Franceschi et al. but differ from those of Abbot et al. who reported increased serum cortisol concentration.

In the light of the present study it seems that subclinical hypofunction of adrenal cortex is not rare in epileptic patients. Diminished adrenocortical activity may be a result of both factors, the influence of the disease itself and the effect of anticonvulsant drugs on biosynthesis and metabolism of cortisol.

This study was presented at 19 Danube Symposium of Neurological Sciences, Heidelberg, October 1986.

References

4 Franceschi M, Pergo L, Cavagnini F, et al. Effect of long-term antiepileptic therapy on the hypothalamic-

Table 2  Mean values of progesterone and cortisol levels in serum and 17-OHCS in urine before and during phenytoin treatment in relation to aetiology and epilepsy course

<table>
<thead>
<tr>
<th>Groups</th>
<th>Aetiology and epilepsy course</th>
<th>Progesterone nmol/l</th>
<th>Cortisol nmol/l</th>
<th>17-OHCS umol/24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>Unknown aetiology</td>
<td>3.67 ± 1.46</td>
<td>451.74 ± 247.37</td>
<td>8.73 ± 4.28</td>
</tr>
<tr>
<td>Before treatment</td>
<td>Known aetiology</td>
<td>3.17 ± 1.46</td>
<td>399.60 ± 191.09</td>
<td>6.49 ± 3.49</td>
</tr>
<tr>
<td>12 months</td>
<td>Mild epilepsy</td>
<td>4.21 ± 1.32</td>
<td>480.04 ± 188.73</td>
<td>7.24 ± 3.36</td>
</tr>
<tr>
<td>24 months</td>
<td>Mild epilepsy</td>
<td>4.48 ± 1.63</td>
<td>446.94 ± 54.59</td>
<td>6.73 ± 3.07</td>
</tr>
<tr>
<td>12 months</td>
<td>Moderate and severe epilepsy</td>
<td>4.03 ± 1.58</td>
<td>484.63 ± 248.67</td>
<td>6.49 ± 3.45</td>
</tr>
<tr>
<td>24 months</td>
<td>Moderate and severe epilepsy</td>
<td>4.32 ± 1.24</td>
<td>502.00 ± 197.72</td>
<td>5.89 ± 3.19</td>
</tr>
</tbody>
</table>

Number of patients in brackets.


8 Rogozea R. Interrelation at plasmatic level between anti-epileptic drugs and lipids. Its implications in the efficiency of treatment in epilepsy. III. Changes induced by phenobarbital or, and diphenylhydantoin in serum lipids, lipoproteins and cortisol. *Neurol Psychiatr (Bucur)* 1982;20:89–100.


